REMARKS/ARGUMENTS

Claim 1-23 are pending in this application and are subject to a Restriction Requirement. Claims 2-8, 1, and 9-19 are examined to the extent that R_3 reads on piperidene. The remaining compounds are withdrawn from consideration without prejudice or disclaimer. Applicant reserves the right to prosecute these compounds in a divisional application. Claim 21 is amended without to recite that the claimed method is for treating breast cancer; the other cancers have been removed without prejudice or disclaimer to further prosecution of this case. Applicant reserves the right to prosecute claims to these in a continuation or divisional application. Claim 23 is canceled without prejudice or disclaimer. Applicant reserves the right to prosecute this claim in a continuation or divisional application. Claims 1-23 are rejected. In view of the amendment and remarks made herein, Applicants respectfully request reconsideration of claims 1-22.

Rejection under 35 U.S.C. § 102(f)

Claims 1-23 are rejected under 35 U.S.C. § 102(f) as anticipated by Kim *et al.* CA 139:117307. Applicant has attached hereto a Declaration under Rule 1.132 (pursuant to *In re Katz* USPQ 14 (CCPA 1982)), signed by Dr. Robert W. Brueggemeier, inventor of the present application. The Declaration explains that Dr. Brueggemeier and Young-Woo Kim are the only inventors of the compounds and methods recited in the claims. James A. Mobley, the other author of the reference, did not invent the claimed compounds or methods. Since Brueggemeier and Kim are the only inventors of the compounds and methods recited in the claims, Applicants respectfully request that this rejection be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claim 1 is rejected under 35 U.S.C. § 103(a) as unpatentable over Chiesi *et al.* (WO 98/29403, hereinafter referred to as "Chiesi") in view of King *et al.* Medicinal Chemistry, pp. 206-209 (hereinafter referred to as "King"). Specifically, the Examiner asserts that one skilled in the art would be motivated to use SO or SO_2 in place of the CO in the compounds of Chiesi based on Table 2 of King. Applicants respectfully disagree.

At best, the King chapter provides an "obvious to try" rationale. While Table 2 of King shows that SO and SO_2 ***may*** be non-classical bioisosteres of CO, the article itself explains the uncertainty involved. First, King explains that bioisosterism can produce "significant changes in selectivity, toxicity, and metabolic stability...." (King, page 207, second full paragraph.) King goes on to state,

> When considering any approach to lead optimization, alteration of one part of the molecule almost always affects more than just one property. Isosteric and bioisosteric replacements are no exception and this should always be considered when analyzing the result of such replacements. For example, a simple CH_2 to O to S series of replacements can alter size, shape, electronic distribution, water or lipid solubility, pK_a, metabolism, or hydrogen bonding capacity, **all with unpredictable effects upon biological activity**."

King, page 209, first full paragraph (emphasis added). Moreover, the King article provides a **rational approach**, which is different from the legal standard of obviousness. Thus, while it may be rational for one skilled in the art to try replacing a carbonyl linker with a thionyl or sulfonyl, the effect on biological activity would be unpredictable. While the King reference discusses bioisosteres, it also points out that even among bioisosteres there is really no reasonable expectation that bioisosteric replacements will yield compounds that maintain the same biological activity. Accordingly, Applicants respectfully submit that claim 1 is non-obvious over Chiesi in view of King.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 20 and 21 are rejected under 35 U.S.C. § 112, first paragraph. The Examiner first noted that the treatment of cancer is highly unpredictable, and the specification provides a description of the efficacy of the compounds in breast cancer cell lines. Claim 21, as amended, recites method for treating, inhibiting, or delaying the onset of a cancer in a subject in need of such treatment; the method comprising administering a therapeutically effective amount of the elected compound for the treatment of breast cancer.

Second, the Examiner questioned the phrase "a method for treating, inhibiting, or delaying the onset of a cancer in a subject in need of such treatment..." asking how one diagnosed with cancer would be able to delay the onset of cancer. Applicant respectfully points to Applicants' specification, paragraph 27 where Applicants discuss how the claimed compounds

may be used in prophylactic treatments by people who have not necessarily developed cancer yet but are at risk of developing cancer. This is further explained in paragraph 29, which explains that people at risk of developing cancer may be at risk due to exposure to carcinogenic agents, being genetically predisposed or may have a precancerous condition. Dosage is discussed in Applicants' specification in paragraphs 28 and 34, for example. Applicant respectfully submits that one skilled in the art would be able to make and use the invention defined by amended claims 20 and 21, and that amended claims 20 and 21 are now in condition for allowance.

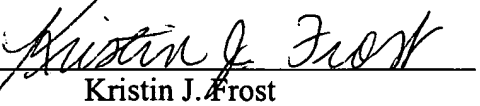
Rejection under 35 U.S.C. § 112, second paragraph

Claim 23 is rejected under 35 U.S.C. § 112, second paragraph. Claim 23 is canceled without prejudice or disclaimer. Accordingly, this rejection is moot.

If issues relating to this application can be resolved by discussion, the Examiner is invited to contact the undersigned attorney by telephone. Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

CALFEE, HALTER & GRISWOLD LLP

By 

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